IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of Tsuyoshi NAGANUMA et al

Application No.: 10/538,514 Confirmation No.: 1878

Filed: June 9, 2005 Group Art Unit: 4133

For: SOLID DRUG FOR ORAL USE

Examiner: Walter E. Webb

DECLARATION UNDER 37 C.F.R 1.132

Honorable Commissioner for Patents

Washington, D.C. 20231

Sir:

I, Tsuyoshi NAGANUMA of 4622-38, Toyoshina, Azumino-shi, Nagano 399-8205 JAPAN, being duly sworn, declare and state:

THAT I am by profession a research chemist having a bachelor's degree in industrial chemistry from Chuo University in March 1990.

THAT I have been employed since April 1990 by Kissei Pharmaceutical Co., Ltd. of 19-48, Yoshino, Matsumoto-shi, Nagano 399-8710 JAPAN and engaged in engineering and research mainly on:

production on drug products in the production department of the same company from April 1990 to September 1990; and then

formulation technology studies on drug products in Central Research Laboratories of the same company from October 1990 up to now.

THAT I am one of co-inventors of the invention disclosed in the above-identified U.S. patent application and hence I am fully familiar therewith.

In order to demonstarate that the present invention is not obvious over Kitazawa in view of Ishihara and in further view of Salpekar and Shar, we have conducted the following experiment.

Experiment

1. Preparation of (1) Capsules of example 1, 2 and Capsule C of the present invention, and (2) comparative capsules of Capsules A, B, F, H, M, 1A, 1B, 2A and 2B

(1) Capsules of example 1, 2 and Capsule C of the present invention, and (2) comparative capsules of Capsules A, B, F, H, M, 1A, 1B, 2A and 2B were prepared for evaluating their dissolution property and manufacturing aptitude.

Example 1

In accordance with the procedures as described in Example 1 on page 34 in the present specification, a capsule of exmple 1 was preparaed as follows.

A mixture of KMD-3213 (320g), D-mannitol (21,504g), partially pregelatinized starch (PCS, 4,160g) and partially pregelatinized starch (Starch 1500, 1,440g) were mixed sufficiently, and kneaded with an appropriate amount of water to granulate. The granulated material was dried using a fluid bed drier at an inlet air temperature of 60 °C until the exhaust air reaches 40 °C, and sieved. A mixture of magnesium stearate (288g) and sodium lauryl sulfate (288g) was added thereto, mixed for 5 minutes, and filled into a capsule shell

to prepare a capsule containing 2.0mg of KMD-3213.

In preparing the capsules of exmple 1, no filling trouble was observed during encapsulating process, and good manufacturing aptitude was achieved.

Example 2

In accordance with the procedures as described in Example 2 on page 35 in the present specification, a capsule of exmple 2 was preparaed as follows.

A mixture of KMD-3213 (640g), D-mannitol (21,184g), partially pregelatinized starch (PCS, 4,160g) and partially pregelatinized starch (Starch 1500, 1,440g) were mixed sufficiently, and kneaded with an appropriate amount of water to granulate. The granulated material was dried using a fluid bed drier at an inlet air temperature of 60 °C until the exhaust air reaches 40 °C, and sieved. A mixture of magnesium stearate (288g) and sodium lauryl sulfate (288g) was added thereto, mixed for 5 minutes, and filled into a capsule shell to prepare a capsule containing 4.0mg of KMD-3213.

In preparing the capsules of exmple 1, no filling trouble was observed during encapsulating process, and good manufacturing aptitude was achieved.

Capsule C

In accordance with the formulation of Capsule C in Table 4 on page 32 in the present specification, a capsule of capusule C was preparaed as follows.

A mixture of KMD-3213 (36g), D-mannitol (1522.8g), and partially pregelatinized starch (Starch 1500, 90g) were mixed sufficiently, and kneaded with an appropriate amount of water to granulate. The granulated material was dried using a fluid

bed drier at an inlet air temperature of 60 °C until the exhaust air reaches 40 °C, and sieved. A mixture of magnesium stearate (9.9g) and sodium lauryl sulfate (9.9g) was added to the granule (1,007.6g), mixed for 5 minutes, and filled into a capsule shell to prepare a capsule containing 4.0mg of KMD-3213.

In preparing the capsules of capsule C, no filling trouble was observed during encapsulating process, and good manufacturing aptitude was achieved.

In order to evaluate the influence of the addition of a lubricant on the dissolution property of capsules and mamufacturing aptitude for preparing capsules, Capsule A not containing any lubricant was compared with Capsules B and H containing magnesium stearate as a lubricant.

Comparative example of capsule A

In accordance with the formulation of Capsule A in Table 4 on page 32 in the present specification, a capsule of Capsule A was preparaed as follows.

A mixture of KMD-3213 (32g), D-mannitol (1,353.6g), and partially pregelatinized starch (Starch 1500, 80g) were mixed sufficiently, and kneaded with an appropriate amount of water to granulate. The granulated material was dried using a fluid bed drier at an inlet air temperature of 60 °C until the exhaust air reaches 40 °C, and sieved. The granule was filled into a capsule shell to prepare a capsule containing 4.0mg of KMD-3213 manually.

In preparing the capsules of capsule A, a filling trouble such as sticking was observed during encapsulating process.

Comparative example of capsule B

In accordance with the formulation of Capsule B in Table 4 on page 32 in the present specification, a capsule of Capsule B was preparaed as follows.

A mixture of KMD-3213 (32g), D-mannitol (1,353.6g), and partially pregelatinized starch (Starch 1500, 80g) were mixed sufficiently, and kneaded with an appropriate amount of water to granulate. The granulated material was dried using a fluid bed drier at an inlet air temperature of 60 °C until the exhaust air reaches 40 °C, and sieved. Magnesium stearate (12.6g) was added to the granule (1,282.4g), mixed for 10 minutes, and filled into a capsule shell to prepare a capsule containing 4.0mg of KMD-3213.

In preparing the capsules of capsule B, no filling trouble was observed during encapsulating process, and good manufacturing aptitude was achieved.

Comparative example of capsule H

In accordance with the formulation of Capsule H in table 5 on page 34 in the present specification, a capsule of Capsule H was preparaed as follows.

A mixture of KMD-3213 (20g), D-mannitol (1,344g), partially pregelatinized starch (PCS, 260g) and partially pregelatinized starch (Starch 1500, 90g) were mixed sufficiently, and kneaded with an appropriate amount of water to granulate. The granulated material was dried using a fluid bed drier at an inlet air temperature of 60 °C until the exhaust air reaches 40 °C, and sieved. Mmagnesium stearate (10.8g) was added to the granule (1,028.4g), mixed for 5 minutes, and filled into a capsule shell to prepare a capsule containing 4.0mg of KMD-3213.

In preparing the capsules of capsule B, no filling trouble was observed during encapsulating process, and good manufacturing aptitude was achieved.

Shar discloses several tablet formulations in the specification of US5,370,878, all of which contains silicon dioxide. In order to evaluate the influence of silicon dioxide on the dissolution property and mamufacturing aptitude, Capsule C of the present invention containing sodium lauryl sulfate was compared with comparative Capsule F containing colloidal silica (light anhydrous silisic acid) instead of sodium lauryl sulfate.

Comparative example of capsule F

A mixture of KMD-3213 (36g), D-mannitol (1522.8g), and partially pregelatinized starch (Starch 1500, 90g) were mixed sufficiently, and kneaded with an appropriate amount of water to granulate. The granulated material was dried using a fluid bed drier at an inlet air temperature of 60 °C until the exhaust air reaches 40 °C, and sieved. A mixture of magnesium stearate (9.9g) and Light Anhydrous Silisic Acid (9.9g) were added to the granule (1,007.6g), mixed for 5 minutes, and filled into a capsule shell to prepare a capsule containing 4.0mg of KMD-3213 manually.

Ishihara discloses tablets of formulation examples 1 to 6 in the specification. All the tablets contain lactose, corn starch and magnesium stearate. Ishihara also describes general mentions regarding dosage forms including capsule; and bulking agent including D-mannitol in the specification.

In order to compare the dissolution rate of the capsule of the present invention with a formulation that may be suggested by Ishihara, we have prepared comparative capsule M

using mannitol instead of lactose acoording to the tablet of Formulation example 1 as described on page 51 of US2002/0177593 as follows.

Comparative example of capsule M

A mixture of KMD-3213 (216.2 g), D-mannitol (7,687 g) and corn starch (1,922 g) were mixed sufficiently. Separately, corn starch (78.24 g) was suspended in water (2,172.8 g), and the suspension was heated at about 80 °C to prepare starch paste. The mixture was granulated with the starch paste. The granule was dried using a fluid bed drier at an inlet air temperature of about 60 °C until the exhaust air reaches 40 °C, and sieved. Magnesium stearate (97.3 g) was added to the sieved granules and mixed for 10 minutes, and the mixture was filled into a capsule shell to prepare a capsule containing 4.0mg of KMD-3213.

In preparing the comparative capsule M, significant adhering onto tamping pin of an encapsulator was observed during encapsulating process.

In order to compare the dissolution rate of the capsule of the present invention with a formulation suggested by Salpekar, we have prepared a capsule containing KMD-3213 instead of acetaminophen; partially pregelatinized starch (Starch 1500); povidone; and stearic acid acoording to the composition of Example 1 as described in Salpekar (US4,757,090) as follows.

Comparative capsule 1A and 1B

A mixture of KMD-3213 (9.0 g), partially pregelatinized starch (0.85 g) and povidone (0.1 g) was mixed sufficiently. The mixture was granulated with water. The granule was dried using a Static Solid bed drier at an inlet air temperature of

about 70 °C for 2 hours, and sieved. Stearic acid (0.05 g) was added to the sieved granules and mixed for 1 minute, and the mixture was filled into a capsule shell to prepare a capsule containing 4.0 mg of KMD-3213 (1A).

Furthermore, sodium lauryl sulfate (0.05 g) was added to the lubricated granules containing stearic acid and mixed for 1 minute, and the mixture was filled into a capsule shell to prepare a capsule containing 4.0 mg of KMD-3213 (1B).

In order to compare the dissolution rate of the capsule of the present invention with a formulation suggested by Shar, we have prepared a capsule containing KMD-3213 instead of acetaminophen; partially pregelatinized starch (Starch 1500); povidone (K-90); croscarmellose sodium (Ac-Di-Sol); stearic acid; and colloidal sillicon dioxide acoording to the composition of Example 1 as described in Shar (US5,370,878) as follows.

Comparative capsule 2A and 2B

A mixture of KMD-3213 (9.0 g), partially pregelatinized starch (0.35 g), croscarmellose sodium (0.2 g) and povidone (0.2 g) was mixed sufficiently. The mixture was granulated with water. The granule was dried using a Static Solid bed drier at an inlet air temperature of about 70 °C for 2 hours, and sieved. Colloidal sillicon dioxide (0.05 g) and stearic acid (0.2 g) were added to the sieved granules and mixed for 1 minute, and the mixture was filled into a capsule shell to prepare a capsule containing 4.0 mg of KMD-3213 (2A).

Furthermore, sodium lauryl sulfate (0.2 g) was added to the lubricated granules containing stearic acid and colloidal sillicon dioxide and mixed for 1 minute, and the mixture was filled into a capsule shell to prepare a capsule containing 4.0

mg of KMD-3213 (2B).

2. Dissolution test

In accordance with the procedures of "Dissolution Test Method" as described in Test example 4 in the present specification, the capsules of example 1, 2 and Capsule C of the present invention; and the comparative capsules of Capsules A, B, F, H, M, 1A, 1B, 2A and 2B were tested. The results are shown in Tables 1 and 2.

Table 1

Capsule	the present invention			Comparative examples				
	Example 1	Example 2	Capsule C	Capsule A	Capsule B	Capsule H	Capsule F	Capsule M
KMD-3213	2.0	4.0	4.0	4.0	4.0	2.0	4.0	4.0
D-Mannitol	134.4	132.4	169.2	169.2	169.2	134.4	169.2	142.2
Partially pregelatinized starch (PCS)	26.0	26.0				26.0		
Partially pregelatinized starch (Starch 1500)	9.0	9.0	10.0	10.0	10.0	9.0	10.0	
Corn starch								37
Magnesium stearate	1.8	1.8	1.8		1.8	1.8	1.8	1.8
Sodium lauryl sulfate	1.8	1.8	1.8					
Light anhydrous silicic acid							1.8	
total weight (mg/capsule)	175.0	175.0	186.8	185.0	185.0	173.2	186.8	185
Dissolution rate (%) after 15 minutes	93	97	85	85	8	23	9	64
Filling problem during encapsulation	none	none	none	sticking	none	none	none	sticking

Table 2

Capsule	the present invention		Comparative Capsule			
	Example 1	Example 2	1A	1B	2A	2B
KMD-3213	2.0	4.0	4.0 (90.0)	4.0 (90.0)	4.0 (90.0)	4.0 (90.0)
D-Mannitol	134.4	132.4				
Partially pregelatinized starch (PCS)	26.0	26.0				
Partially pregelatinized starch (Starch 1500)	9.0	9.0	0.378 (8.5)	0.378 (8.5)	0.156 (3.5)	0.156 (3.5)
Croscarmellose Sodium (Ac-Di-Sol)					0.089 (2.0)	0.089 (2.0)
Povidone (K-30)			0.044 (1.0)	0.044 (1.0)		
Povidone (K-90)					0.089 (2.0)	0.089 (2.0)
Magnesium stearate	1.8	1.8				
Sodium lauryl sulfate	1.8	1.8		0.022 (0.5)		0.089 (2.0)
Stearic acid			0.022 (0.5)	0.022 (0.5)	0.089 (2.0)	0.089 (2.0)
Colloidal sillicon dioxide					0.022 (0.5)	0.022 (0.5)
total weight mg/capsule	175.0	175.0	4.444 (100.0)	4.466 (100.5)	4.445 (100.0)	4.534 (102.0)
Dissolution rate (%) after 15 minutes	93	97	9	16	12	16

numeric value in parentheses: ratio

As a result of dissolution test shown in Tables 1 and 2, it was suggested the following:

(1) Comparison of Capsule A not containing any lubricant with Capsules B and H containing magnesium stearate as a lubricant shows that the dissolution rate of Capsules B and H containing magnesium stearate was notably lower than that of Capsule A. It is apparent that use of magnesium stearate as a lubricant influenced the compositions containing the lubricant to increase their dissolution time.

General mention regarding lubricants on column 3, lines 3 to 9.in Salpekar, fails to teach or suggest what kind of lubricants could be used for providing compositions containing KMD-3213 with immediate dissolution properties.

(2) Comparison of Capsule C of the present invention containing sodium lauryl sulfate with comparative example F containing silicic acid instead of sodium lauryl sulfate shows that the dissolution rate of Capsule F is notably lower than that of Capsule C of the present invention.

Shar fails to teach or suggest what kind of lubricants could be used for providing compositions containing KMD-3213 with immediate dissolution properties.

(3) Comparison of Example 1 and Capsule C of the present invention with Capsules H and B of comparative examples in Table 1 shows that blending partially pregelatinized starch with KMD-3213 in Capsules H and B does not impart immediate dissolution at all. Furthermore, comparison of Capsule H with Capsule M shows that blending partially pregelatinized starch in place of corn starch with KMD-3213, makes the dissolution of Capsule H worse. These results shows clearly that immediate

dissolution properties cannot be achieved by only using partially pregelatinized starch.

It is apparent that the general mention regarding partially pregelatinized starch in Salpekar does not teach the immediate dissolution property exhibited by the capsules of the present invention.

(4) The examiner stated in the office action that the comparative example in the 132 declaration submitted on December 1, 2008, is improper since we used 22 and 45 times more KMD-3213 in the compositions of the comparative examples. However, in the dissolution test of the Declaration, we have used comparative capsules 1A, 1B, 2A and 2B containing the same amount of KMD-3213 (4.0mg/capsule) as example 2 of the present invention, which are shown again in Table 2 of this Declaration.

Regarding the amount and ratio of KMD-3213 and partially pregelatinized starch to the total weight of compositions, we have also compared the dissolution rate of example 1 with that of capsule H, both of which contain the same amount and ratio of KMD-3213, mannitol and partially pregelatinized starch. The results show clearly that the dissolution rate of the capsule of comparative capsule H has notably lower dissolution rate than that of example 1 of the present invention.

The results of the dissolution test on Capsules 1A, 2B, 2A and 2B in Table 2 also indicate that all of the comparative capsules showed only less than 20% dissolution.

It is apparent that the general mention regarding partially pregelatinized starch in Salpekar does not teach the immediate dissolution property exhibited by the capsules of the present invention.

(5) The dissolution test on Capsule M showed a moderate dissolution rate of 64%, but filling problems such as sticking during encapsulating process was observed in the manufacture of Capsule M. Therefore, we cannot prepare Capsule M in a manufacturing scale. Substituting partially pregelatinized starch for corn starch results in the improvement of filling problem during encapsulating process. On the contrary, use of partially pregelatinized starch instead of corn starch makes the dissolution of Capsules B and H worse notably.

Ishihara fails to teach or suggest how to achieve immediate dissolution properties and good manufacturing aptitude without causing filling problems during encapsulating process at the same time.

As discussed above, Kitazawa, Ishihara, Salpekar and Shar fail to teach or suggest how to improve dissolution properties in water in which KMD-3213 is hardly soluble and how to resolve filling problems caused by the cohesive property of KMD-3213 during encapsulating process at the same time.

Therefore, we believe that the capsules of the present invention are not obvious over Kitazawa in view of Ishihara and in further view of Salpekar and Shar.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of the Title 18 of the United States Code and such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

June 23, 2009

Tsuyoshi Naganuma

Tsuyoshi NAGANUMA